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Unveiling the Chemistry of E-Cigarettes: What's Inside Your Vape?

Running title: Chemical Composition of E-Cigarettes

Milijana M. Zlatković* **and Mihajlo A. Halilović,**

University of Niš, Faculty of Sciences and Mathematics, Department of Chemistry, Višegradska 33, 18000 Niš, Serbia

Milijana Zlatković: milijana.zlatkovic@pmf.edu.rs
Mihajlo Halilović: mihajlo.halilovic@pmf.edu.rs.

* milijana.zlatkovic@pmf.edu.rs

ABSTRACT

Smoking tobacco represents one of the most harmful habits for health, causing addiction, a series of somatic problems ranging from allergic reactions to cardiovascular diseases and lung cancer. Recently, electronic cigarettes (e-cigarettes) are increasingly being promoted as a healthier alternative to smoking. Though e-cigarettes have been marketed as safer alternatives to traditional tobacco products, the composition of e-liquids, the substances inhaled during vaping, require critical evaluation. E-liquids typically contain nicotine, propylene glycol, glycerol, flavoring agents, and other additives. However, studies have identified harmful constituents, including tobacco-specific nitrosamines (TSNAs), a group of carcinogenic compounds found in tobacco and tobacco smoke, volatile organic compounds (VOCs), heavy metals, and carbonyl compounds, which can form during heating.

Nicotine, a primary component of most e-liquids, poses addiction risks and cardiovascular effects. TSNAs and VOCs, even in trace amounts, are known carcinogens. Heavy metals (lead, cadmium, and nickel) released from e-cigarette components raise toxicological concerns. It's important to note that when inhaled, flavoring agents, often considered safe for ingestion, may have adverse respiratory effects, underscoring the need for caution.

Despite their popularity, e-cigarettes' long-term health impacts remain largely unknown, complicating public health assessments (Omaiye et al., 2020). The diverse chemical composition of e-liquids, combined with the alarming lack of strict quality standards, raises additional concerns. Present review emphasizes the urgent need for comprehensive research into the components of e-liquids and their potential health effects. Regulatory frameworks should introduce mandatory declarations of ingredient and product safety to reduce the risks associated with e-cigarette use. Addressing these gaps is essential to inform consumers, guide policymakers, and ensure public health protection amidst the growing popularity of e-cigarettes.

Keywords: *e-cigarettes, nicotine, tobacco-specific nitrosamines, volatile organic compounds, carbonyls, heavy metals*

Introduction

Electronic cigarettes represent battery-powered devices that intend to simulate standard tobacco cigarettes by converting e-liquid into an inhalable aerosol. This e-liquid can be contained in a disposable cartridge or tank, allowing consumers to refill it as needed. Because they do not burn tobacco, it is expected that they do not produce the same number of chemicals that can be found in conventional tobacco products. With that in mind, they can be proposed as potential products for tobacco harm reduction (Bullen et al., 2013; Capponeto et al., 2013a,b; Etter et al., 2011; Farsalinos et al., 2013a,b; Manzoli et al., 2013; O'Connor et al., 2012; Polosa et al., 2013). While their safety and efficacy as a substitute for standard tobacco cigarettes are controversial, many available studies are suggesting the potential of these products in the promotion of smoking reduction. Over the last few years, there have been numerous concerns regarding these products' manufacturing processes and quality since used e-liquids are not manufactured to standards such as those regarding medications. The constituents of cartridges and refill e-liquids could not comply with the label. They could contain impurities or many toxic substances (Etter et al., 2013; O'Connor et al., 2012).

E-liquids, the substances used in e-cigarettes, consist of nicotine (in different concentrations) in a mixture of vegetable glycerine and/or propylene glycol with water, followed by many other constituents (Omaiye et al., 2020; Krüsemann et al., 2021). Nicotine, a highly addictive substance, is the primary component that makes e-cigarettes appealing to smokers. When heated by an atomizer, the alcohols mentioned are used as humectants for aerosol creation. A wide variety of different chemicals are added for the flavor and aroma. As the usage of e-cigarettes requires heating the e-liquid, a variety of new chemical compounds can be produced, and many of them can be considered harmful.

The very first tests on the chemical composition of e-cigarette liquids were performed way back in 2008 by Health New Zealand Ltd. (Laugesen, 2008). After one year, the Food and Drug Administration Agency (FDA) was asked to quantitate the amount of nicotine and impurities in two brands of e-cigarette cartridges, which highlighted the presence of low amounts of nicotine in liquids labeled as 'no nicotine'. The same report showed the presence of toxic compounds as impurities, one of them being diethylene glycol. The presence of tobacco-specific nitrosamines, potent human carcinogens, was also highlighted (IARC Monogr., 2007). Moreover, some studies reported compounds such as formaldehyde, acetaldehyde, and acrolein in small amounts (Etter et al., 2013; Laugesen M., 2008). In contrast, others reported the presence of other volatile organic compounds such as benzene, toluene, xylene, and styrene (Etter et al., 2013; FDA. Laboratory analysis of electronic cigarettes conducted by FDA. 2009; Goniewicz et al., 2014b). Although e-cigarettes contain various metal components, many metals have been found in the e-liquids and aerosol. More recent data has shown that differences between nicotine content and labels are more minor than previously reported, suggesting an improvement in manufacturing (Davis et al., 2014; Etter et al., 2013).

Nicotine and tobacco-specific nitrosamines

Nicotine is a highly addictive central and peripheral nervous system stimulant with a lethal dose estimated to be 0.8-1.0 *mg/kg* of body weight in adult nonsmokers (Etter et al., 2011; Yildiz et al., 2004). Because it is both toxic and addictive, it is essential that its content in refill liquids and cartridges comply with the label (Davis et al., 2014). Nicotine used for e-liquid production is extracted from tobacco. Its extraction, however, can be followed by the production of some tobacco-specific nitrosamines (TSNAs), such as N-nitrosonornicotine, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, N-nitrosoanatabine and N-nitrosoanabasine. They are believed to be highly toxic (FDA. Laboratory analysis of electronic cigarettes conducted by FDA. 2009). Other impurities that can be found are minor alkaloids like nornicotine, anatabine, anabasine, myosmine, cotinine, nicotine-N'-oxides (*cis* and *trans* isomers), β-nicotyrine and β-nornicotyrine (Etter et al., 2013). Nicotine and cotinine in tobacco are mainly present as the levorotary *(S)*-isomers (only 0.1%–0.6% of total nicotine content is *(R)*-nicotine). In contrast, anabasine, anatabine, and nornicotine in tobacco exist as a mixture of enantiomers (Omaiye et al., 2020) According to European Pharmacopeia, nicotine of pharmaceutical grade may, as raw material, contain up to 0.3% of each of the specified nicotine impurities. However, since the e-liquid manufacturing process is not strictly controlled, some products can show impurities above these acceptance limits for pharmaceutical products. For both compound types, methods such as HPLC-DAD, GC-MS, and LC-MS/MS have shown reliable results and can be used for regular content assessment.

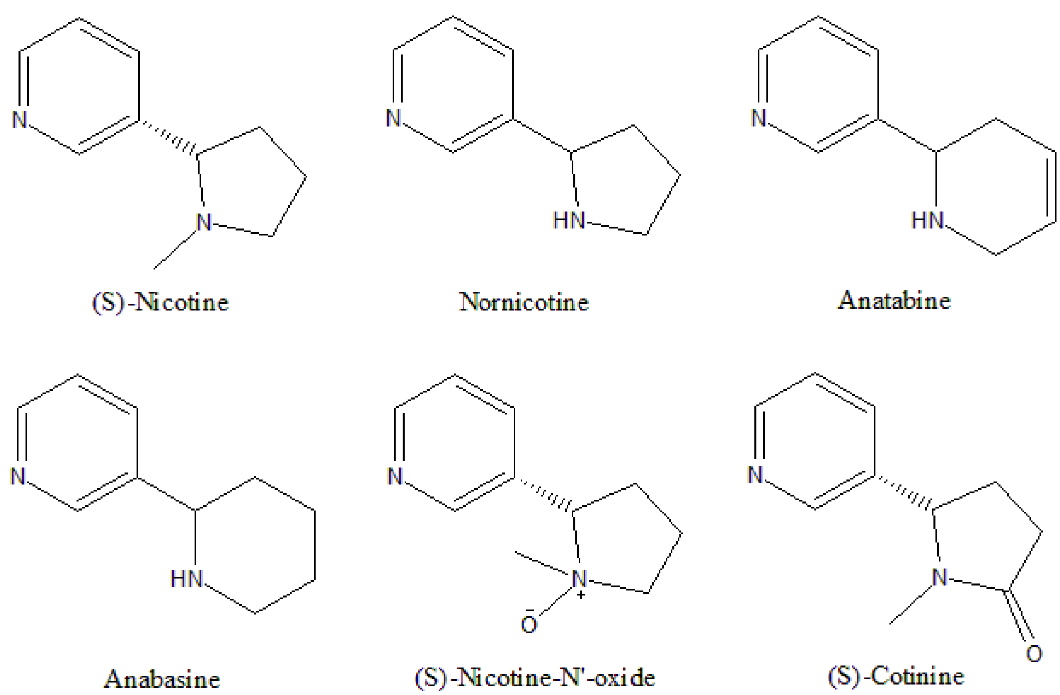

Figure 1. Structures of nicotine and nicotine related compounds that are most abundant in e-liquids.

Glycols used as humectants

E-liquids, containing propylene glycol, vegetable glycol, or a combination of both, are designed to generate aerosol upon heating (Laugesen, 2008). Both glycols have been marked as 'generally safe' by the FDA and GRAS, making them approved solvents 59oru se in pharmacy. This safety reassurance should leave the audience with a sense of security about the composition of e-liquids. Vegetable glycol is derived from plant oils, while propylene glycol is prepared by hydrolysis of propylene oxide under pressure at high temperatures. Unlike inhalers or nebulizers, which can use the mentioned glycerols, e-cigarettes consist of a heating component, and the heating of glycols can generate various potentially toxic carbonyl compounds. One of the tests for propylene glycol identification in pharmaceutical products requires using a GC/FID method, and the reported chromatographic parameters can also be used to determine propylene glycol content on e-liquids. Chromatographic separation was achieved using a column coated with 14% cyanopropylphenyl-86% methylpolysiloxane stationary phase. Additionally, these components can be easily identified by ^{1}H NMR spectroscopy after purification and confirmed by GC-MS. Rest assured, these components are safe 59oru se in e-liquids.

Volatile organic compounds and carbonyls

Volatile organic compounds are a group of various compounds usually recognized as harmful to human health. They have high vapor pressure, low-to-medium water solubility, and low molecular weight (Moran et al., 2006). Published results (Laugesen, 2008; Lim et al., 2013; Uchiyama et al., 2013) demonstrated the presence of small amounts of formaldehyde and acetaldehyde in some cartridge liquids. Acetaldehyde may occur in some liquids because of its intentional addition as a flavor compound. The International Agency for Research on Cancer [IARC] classified formaldehyde as carcinogenic to humans (group 1) and acetaldehyde as possibly carcinogenic to humans (group 2B). Acrolein can irritate the nasal cavity and damage the lining of the lungs. Benzene (group 1 by IARC) and other solvents (toluene, xylenes, and styrene) could be present in e-liquids because of their use as solvents for nicotine extraction from tobacco leaves (Etter et al., 2013). Other volatile organic compounds in the liquid phase produce aromas and flavor through heating (Bahl et al., 2012). For analysis of these compounds, GC-MS can use the Environmental Protection Agency (EPA) method 826030. The chemical composition of aerosol can be different from liquid: using e-cigarettes requires heating the liquid, and under such conditions, chemical reactions may result in the formation of new compounds. In some models, the temperature measured in the center of the heating coil can be notably high (≥ 350 °C), promoting pyrolysis reactions of e-liquid chemical components (Moran et al., 2006). Many studies report that short-chain aldehydes (formaldehyde, acetaldehyde, and acrolein) are formed under the heating of e-liquids (Etter et al., 2013; Laugesen, 2008; Schober et al., 2013, Uchiyama et al., 2020). Uchiyama et al. (2013) demonstrated that 70% of examined e-cigarette brands generated formaldehyde, acetaldehyde, and acrolein with maximum concentrations of 260, 210, and 73 mg/m^3, respectively. They also detected two toxic carbonyl compounds, glyoxal, and methylglyoxal, which, until now, have not been detected in the smoke from tobacco cigarettes.

Heavy metals

Studies concerning the quantification of metals in refill liquids show that their content doesn't exceed limits that harm human health (Burstyn et al., 2014). In Ruyan's report (Laugesen, 2008) cartridge liquids were tested for heavy metals. Still, none of them was found at a concentration higher than 0.1–0.2 ppm. Since e-cigarettes contain various metal components, metals can migrate to the generated aerosol, constituting a health risk to users and bystanders. Williams et al. (2013) showed that small particles comprised of various elements (Sn, other metals, semimetals, and silicate) passed through cartomizer fibers and were present in the aerosol of e-cigarettes. A total of 22 elements were identified in aerosol, including Pb, Ni, and Cr. Pb and Cr concentrations in aerosol were within the range of conventional cigarettes (Zhao et al., 2023). In contrast, Ni concentration was about 2–100 times higher in e-cigarette aerosol than in Marlboro brand cigarettes. Ni particles likely originated from the nichrome wire. Significant amounts of Sn, other metals, and silicate beads escaped into an aerosol. They would result in human exposure, which, in some cases, is probably more remarkable than those observed in a conventional cigarette. All of the mentioned metals were determined through validated ICP-OES or ICP-MS methods (Laugesen, 2008; Williams et al., 2013.).

Table 1. Published and approved analytical methods for various components of e-liquids analysis

Analytes / classes of analytes	Matrices	Analytical techniques	References
Nicotine	Refill liquid	GC/FID, HPLC/DAD	Schober et al., 2013; Davis et al., 2014.
	Cartridge[a]	GC/FID, HPLC/UV	Cheah et al., 2014; Westenberger et al., 2009.
Nicotine and nicotine related compounds	Cartridge, aerosol	GC-TSD	Goniewicz et al., 2014a,b.
	Cartridge	HSGC-MS	Westenberger et al., 2009
	Cartridge[a], refill liquid, aerosol	HPLC/DAD	Trehy et al., 2011.
Tobacco specific nitrosamines	Cartridge[a]	LC-MS/MS	Laugesen , 2008; Westenberger et al., 2009
	Refill liquid	LC-MS/MS	Schober et al., 2013; Kim et al., 2013.
Propylene glycol	Refill liquid	GC/FID (GC/MS[b])	Etter et al., 2013.
Volatile organic compounds	Refill liquid	GC-MS (^{1}H NMR[b])	Schober et al., 2013
Carbonyl compounds	Refill liquid	HS-SPME GC-MS[c]	Lim et al., 2013.
	Aerosol	HPLC/DAD[c]	Goniewicz et al., 2014a,b; Kosmider et al., 2014.
Heavy metals	Cartidge[a]	ICP-MS	Laugesen , 2008
	Aerosol	ICP-MS, ICP-OES	Goniewicz et al., 2014b; Williams et al., 2013

[a] It requires extraction with organic solvent; [b] Confirmatory method; [c] Derivatization step previously

Conclusion

Electronic cigarettes (e-cigarettes) are a complex technological alternative to traditional tobacco products, offering potential harm reduction benefits due to the absence of combustion. However, the safety of e-cigarettes remains controversial, with concerns over manufacturing standards, impurities, and possible harmful byproducts. E-liquids, composed primarily of nicotine, glycols, and flavor additives, can contain toxic substances such as tobacco-specific nitrosamines, carbonyl compounds, volatile organic compounds, and heavy metals. While some improvements in product consistency and manufacturing quality have been noted, significant variability still persists. It is crucial to assess the composition and potential risks associated with e-cigarettes using comprehensive chemical analyses and advanced techniques, such as GC-MS, LC-MS/MS, and ICP-MS. This emphasis on vigilance is key to understanding the health implications of e-cigarettes and ensuring the safety of their users

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